Remarks

I. Status of the Application

Claims 6, 9 and 11 are amended herein. Claims 11 and 12 have been withdrawn from consideration. As a result, claims 1-10 are currently pending and under examination.

II. Claim Objections

Claims 6 and 9 have been objected to under 37 CFR 1.759(c) as being in improper dependent form. This objection has been rendered moot by the amendment of claims 6 and 9 to make them dependent from claim 1 alone.

III. Claim Rejections – 35 USC Section 102

A. Rejection Based on Walz et al.

Applicants traverse the rejection of claims 1-5, 7, 8 and 10 as being anticipated by Walz et al. US 2002/0106332 ("the Walz reference"). Reconsideration and withdrawal of the rejection are respectfully requested in view of the following remarks.

Claim 1 (the only independent claim currently pending) recites a process for preparing a medicament comprising the steps of:

(a) combining a pharmaceutically active ingredient in the form of an agglomerate of primary particles having an agglomerate particle size such that the agglomerate is capable of passing through a sieve having a mesh of 50-3000 μm with a pharmaceutically acceptable particulate carrier, and

(b) mixing the resultant material in a mixer to break up the agglomerate into primary particles dispersed in a pharmaceutically acceptable particulate carrier such that 90% or more of the pharmaceutically active ingredient exists as primary particles having a particle size of 50 μm or less.

The process of claim 1 is neither taught nor suggested by the Walz reference. The Walz reference, like the invention of the present application, relates to a process for producing a powder medicament. The Walz process comprises providing alternating layers of smaller medicament particles and larger carrier particles in a mixer, followed by mixing (paragraphs [007] and [008]). Example 1 at paragraph [0064] explains that the active ingredient tiotropium bromide is passed through a granulating sieve of size 0.5 mm into the mixing container. However, in contrast to the process of Applicants' claim 1, Walz does not disclose that the active ingredient is in the form of an agglomeration of primary particles. Rather, the tiotropium bromide of Walz Example 1 is in micronized form (paragraph [0063]). The sieve size

specified in Applicants' claim 1 characterizes the size of the agglomerates produced. Walz teaches a process that sieves the micronized particles. However, this sieving would not reasonably lead to the formation of an agglomerate of primary particles. Thus, claim 1 is novel over the Walz reference at least for this reason.

Furthermore, the mixing process of the Walz reference is not the same as the mixing step (b) of Applicants' claim 1. The recited mixing step (b) specifically requires that the agglomerated active ingredient is broken up into primary particles dispersed in the carrier, such that 90% or more of the pharmaceutically active ingredient exists as primary particles having a particle size of 50 μm or less. Walz discloses neither the particle size of the active ingredient after the mixing step, nor that the mixing technique is such that the agglomerates of the active ingredient are broken up. This is significant in that it highlights that the active ingredient particles of the reference were not present as agglomerates prior to mixing. For both of the reasons discussed above, Applicants' claim 1 is novel over the Walz reference.

Claims 2-10 depend from claim 1 and incorporate all of the limitations of the base claim. Accordingly, the dependent claims are also not anticipated by the Walz reference.

B. Rejection Based on Bystrom et al.

Applicants traverse the rejection of claims 1-5, 7, 8 and 10 as being anticipated by Bystrom et al. US 6,045,828 ("the Bystrom reference"). Reconsideration and withdrawal of the rejection are respectfully requested in view of the following remarks.

The Bystrom reference discloses a proliposome powder for inhalation comprising an active agent and a lipid (abstract). Following freeze-drying of a solution of active agent and lipid, the resultant powder may be sieved (column 5, lines 20-23). The powder may then be agglomerated into small spheres preferably not larger than 1 mm (column 5, lines 56-63). This method is different from the claimed process. Bystrom discloses agglomeration, but crucially, Bystrom specifically teaches an agglomeration containing both active agent and lipid. In contrast, step (a) of Applicants' claim 1 requires an agglomerate of the active ingredient only, which agglomerate is then mixed with the carrier. The Bystrom reference discloses deagglomeration at column 5, lines 61-63. However, this is the well-known deagglomeration which occurs in the inhalation device, i.e. just prior to inhalation by the patient. In contrast, the mixing step (b) of claim 1 effects deagglomeration in the mixer, i.e. prior to filling of the inhalation device. Therefore, Bystrom fails to disclose (1) a mixing step to break up an agglomerate of primary particles of the pharmaceutically active ingredient, and (2) the breaking

up of the agglomerate into the particle sizes recited in step (b) of claim 1. Thus, claim 1 is not anticipated by the Bystrom reference.

Claims 2-10 depend from claim 1 and incorporate all of the limitations of the base claim. Accordingly, the dependent claims are also not anticipated by the Bystrom reference.

C. Rejection Based on Lizio et al.

Applicants traverse the rejection of claims 1-5, 7, 8 and 10 as being anticipated by Lizio et al. US 2002/0106332 ("the Lizio reference"). Reconsideration and withdrawal of the rejection are respectfully requested in view of the following remarks.

The Lizio reference discloses a process for preparing powder mixtures for inhalation in which no binder is used (paragraph [0002]). The method involves grinding the active ingredient at low temperature in the form of a suspension, mixing with a carrier, and then isolating the powder by evaporation. The resulting powder is then passed through a sieve of size 0.1 to 0.5 mm (paragraph [0010]). Lizio does not teach the mixing of an agglomerate of active ingredient with a carrier, much less of the mixing of an agglomerate of active ingredient with the size required in step (a) of claim 1. Lizio's sieving step is taught as merely removing the grinding beads (paragraph [0013]) after the grinding step, and does not produce an agglomerate. Further, Lizio's sieving step is carried out after the active ingredient and carrier have been mixed in suspension. Moreover, Lizio discloses neither a mixing step which breaks up agglomerated primary particles of active ingredient, nor ANY agglomeration of primary particles of active ingredient at all. Thus, claim 1 is not anticipated by the Lizio reference.

Claims 2-10 depend from claim 1 and incorporate at least all of the limitations of the base claim. Accordingly, the dependent claims are also not anticipated by the Lizio reference.

D. Rejection Based on Backstrom et al.

Applicants traverse the rejection of claims 1-5, 7, 8 and 10 as being anticipated by Backstrom et al. US 5,518,998 ("the Backstrom reference"). Reconsideration and withdrawal of the rejection are respectfully requested in view of the following remarks.

The Backstrom reference relates to the provision of a dry powder for inhalation comprising insulin and a carrier which enhances absorption in the lungs (column 2, third paragraph). Example 1 outlines the method by which such mixtures are obtained. Insulin and sodium caprate are mixed in solution, followed by evaporation to provide a solid. This solid is then crushed, passed through a 0.5 mm sieve, and micronized. This method does not start with an

agglomerate of active ingredient of defined size, nor does it include mixing of this agglomerate with a carrier and breaking up the agglomerate. Finally, the Backstrom reference does not disclose the dispersion of active ingredient with the carrier having the defined particle sizes as recited in Applicants' claim 1. The Backstrom reference discusses agglomerates at column 9, lines 31-39, but this disclosure pertains to agglomeration of the active ingredient and carrier. Also, the deagglomeration referred to by Backstrom is the deagglomeration which occurs in the inhalation device, and not deagglomeration in the mixer. Claim 1 thus is novel over the Backstrom reference.

Claims 2-10 depend from claim 1 and incorporate at least all of the limitations of the base claim. Accordingly, the dependent claims are also not anticipated by the Backstrom reference.

IV. Claim Rejections – 35 USC Section 103 (Rejections Based on the Walz, Bystrom and Lizio References)

Applicants traverse the rejections of claim 2 as obvious over each of the Walz reference, the Bystrom reference, and the Lizio reference. Reconsideration and withdrawal of the rejections are respectfully requested in view of the following remarks.

Claim 2 depends from claim 1 and thus includes at least all of the limitations as the base claim 1. As explained above in Section III of this Amendment, neither the Walz reference, the Bystrom reference or the Lizio reference anticipates claim 1. Moreover, the invention of claims 1-10 would not have been obvious to an ordinarily skilled person from any of the cited references, either alone or in combination.

As way of background, the Applicants were faced with the the problem of providing a powder medicament dispersion of an active ingredient in a carrier with greater homogeneity and lower adhesion between the active ingredient and carrier (paragraph [0005] of the published application US 2008/0131518). It was found that by providing the active ingredient in the form of an agglomerate of primary particles of defined size prior to mixing with the carrier, followed by mixing such that the agglomerate breaks up and disperses in the carrier, both of these advantages can be achieved.

Table 1 of the application illustrates the homogeneity of various blends of budesonide and lactose. Blends 1 and 3 were produced in accordance with claim 1, i.e. the budesonide was agglomerated prior to mixing with the lactose. It can be seen that the %RSD values for blends 1 and 3 are superior to blends 2 and 4, in which the budesonide was not first agglomerated.

The % recovery of these blends are also improved. Table 2 shows the same trend for a different drug, formoterol.

Table 5 shows how the delivered dose, or fine particle fraction (FPF) of etiprednol dicloacetate is improved by using the method of claim 1, when compared to the results of Table 3, where the active ingredient was not first agglomerated.

None of the cited references disclose the agglomeration of the active ingredient prior to mixing with a carrier. The only documents to mention agglomeration at all are the Bystrom and Backstrom references; however, the agglomeration in these instances relate to agglomeration of active ingredient and carrier after mixing, not of the active ingredient prior to mixing with the carrier. Further, the deagglomeration steps disclosed in these documents refer to the deagglomeration which occurs in the inhalation device itself, rather than during the processing of the medicament that will later be added to the inhalation device. This is clearly distinct from the breaking up of the agglomerate in step (b) of claim 1. None of the cited references teach or suggest the specific steps of claim 1. Moreover, the ordinarily skilled person would not have considered preparing an agglomerate of the active ingredient prior to mixing with the carrier, and then breaking up the agglomerate to disperse the active ingredient in the carrier. In the art, absent any teaching to the contrary, this extra step would be seen as an unnecessary increase in processing cost and time. There is no suggestion in the prior art that the claim 1 process would increase dispersal and reduce the adhesion between active ingredient and carrier.

In addition, Applicants respectfully submit that the obviousness analysis since the Supreme Court holding in *KSR* (*KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 127 S.Ct. 1727), has emphasized a need for showing the the skilled person would derive some level of predictability or reasonable expectation of success from the prior art. The cited references fail to disclose:

- an agglomerate of the active ingredient prior to mixing with a carrier; or
- a step of breaking up that agglomerate into primary particles dispersed in a pharmaceutically acceptable particulate carrier.

As discussed previously, Applicants believe that the skilled person would not have been motivated by the cited references to modify the prior art in a way that would generate the above elements of the claimed process. But in addition, Applicants maintain that the references of record would not have provided the indicia of *predictability* or *reasonable expectation of*

success that were weighed by the Supreme Court in KSR (and later incorporated into the examination guidelines of MPEP 2141[1]).

Based on the brief discussion above, Applicants respectfully maintain that *prima facie* obviousness has not been established for claim 2 over the references of record. Claim 2 is therefore patentably unobvious over the cited references. Moreover, independent claim 1 and dependent claims 3-10, though not included in the obviousness rejection, also would not have been obvious to an ordinarily skilled person for at least the reasons discussed above.

V. Conclusion

The application is believed to be in condition for allowance and early favorable action thereon is respectfully requested. In the event any issues remain open, the Examiner is encouraged to contact Applicants' legal representative at the telephone number listed below.

Respectfully submitted,

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The Director is hereby authorized to charge or credit Deposit Account No. **18-0350** for any additional fees, or any underpayment or credit for overpayment in connection herewith.

[1] (A)Combining prior art elements according to known methods to yield predictable results;
(B) Simple substitution of one known element for another to obtain predictable results;
(C) Use of known technique to improve similar devices (methods, or products) in the same way;
(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
(E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;
(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.